CORRELATION OF SERUM URIC ACID WITH PRECLINICAL TARGET ORGAN DYSFUNCTION IN HYPERTENSIVE POPULATION

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CERTIFICATE

This is to certify that the dissertation entitled **"CORRELATION OF SERUM URIC ACID WITH PRECLINICAL TARGET ORGAN DYSFUNCTION IN HYPERTENSIVE POPULATION"** is an original work done by **Dr. SUBRAMANIAN. K** in the Institute of Internal Medicine, Madras Medical College, Government General Hospital, Chennai 03 to be submitted to the Tamil Nadu Dr. M.G.R Medical University, in partial fulfillment of the university rules and regulations for the award of **MD Degree Branch1 General Medicine,** under our supervision and guidance, during the academic period from **July 2003** to **September 2006.**

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CONTENTS

CORRELATION OF SERUM URIC ACID WITH PRECLINICAL TARGET ORGAN DYSFUNCTION IN HYPERTENSIVE POPULATION

Introduction:

Serum uric acid (SUA) plays a role in the development of cardiovascular morbidity in the general population, [1–4] as well as in patients with hypertension, [5–7] type II diabetes,[8] and cardiac or vascular diseases as illustrated by a number of studies. A meta-analysis of data taken from 8 trials that were performed on hypertensive patients showed that each standard deviation (SD) increment in SUA entails an augmentation of cardiovascular risk that equals what is observed for similar changes in blood pressure or total cholesterol.[9] However, the independent role of SUA as a risk factor has been undergoing debate for years. In fact, mild hyperuricemia is often a concomitant finding of obesity, lipid abnormalities, and insulin resistance, all of which are components of the metabolic syndrome (MS). Accordingly, in some studies on white as well as Asian populations, the direct relationship that is observed between uric acid and cardiovascular mortality weakens or disappears after adjusting for confounding factors.[10]

Several pathophysiological mechanisms linking SUA to cardiovascular damage at the cellular and tissue level have been proposed, including proliferation of vascular smooth muscle cells,[11] stimulation of the inflammatory pathway,[12] and possible prothrombotic effects mediated by platelet

activation.[13] In addition, uric acid has proved to be an excellent marker for tissue ischemia and endothelial dysfunction[14] and it has been shown to play a role in the development of atherosclerotic lesions.[15]

The presence of sub-clinical hypertensive organ damage signals a condition of increased risk for cardiovascular, renal, morbidity and mortality. Thus, the search for left ventricular hypertrophy (LVH), carotid atherosclerosis, and microalbuminuria, which are likely to reflect both the severity of blood pressure load and other non-hemodynamic risk factors, is currently recommended as part of global risk assessment.[16] Because the role of SUA in the development of cardiovascular disease is receiving growing attention, a better understanding of its relationship with sub-clinical hypertensive target organ damage (TOD) may help clarify the pathophysiological mechanism(s) underlying this association.

AIM OF THE STUDY

To evaluate the correlation between serum uric acid levels (SUA) and the presence and degree of pre-clinical organ damage in hypertensive population.

TYPE OF STUDY

Cross sectional study

LITERATURE REVIEW

Uric acid, a product of purine metabolism, is degraded in most mammals by the hepatic enzyme, urate oxidase (uricase), to allantoin, which is freely excreted in the urine. However, during the Miocene epoch (2 to 5 million years ago), 2 parallel but distinct mutations occurred in early hominoids that rendered the uricase gene nonfunctional. As a consequence, humans and the great apes have higher uric acid levels (>2 mg/dl) compared with most mammals (<2 mg/dl).

Uric acid levels also vary significantly within humans as the result of factors that increase generation (such as high purine or protein diets, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decrease excretion. A reduction in glomerular filtration rate (GFR) increases serum uric acid, although a significant compensatory increase in gastrointestinal excretion occurs.[20] Hyperuricemia also may result from increased net tubular absorption. After filtration, uric acid undergoes both reabsorption and secretion in the proximal tubule, and this process is mediated by a urate/anion exchanger and a voltage-sensitive urate channel.[21,22] Organic anions such as lactate decrease urate secretion by competing for urate through the organic anion transporter, whereas several substances, including probenecid and benziodarone, have opposite effects.[23]Hyperuricemia is usually defined as >6.5 or 7.0 mg/dL in men and >6.0 mg/dL in women.

Hyperuricemia Is Increased in Subjects at Cardiovascular Risk

Serum uric acid is frequently elevated in subjects at cardiovascular risk[24] Uric acid is higher in men and postmenopausal women because estrogen is uricosuric.[25] In subjects with obesity, insulin resistance, and dyslipidemia ("the metabolic syndrome"), hyperuricemia frequently occurs because insulin stimulates sodium and urate reabsorption in the proximal tubule.[25] Uric acid is increased in subjects with renal disease as the result of reduction in GFR and renal urate excretion. Diuretics, such as thiazides, increase serum uric acid by stimulating both sodium and urate reabsorption in the proximal tubule. Alcohol intake results in elevated uric acid levels due to increased urate generation (from increased adenine nucleotide turnover) and decreased excretion (due to lactate blocking tubular transport of urate).[26,27]

Uric acid is also commonly associated with hypertension. It is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in >75% of subjects with malignant hypertension.[28] The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption.[29] Hypertension also results in micro vascular disease, and this can lead to local tissue ischemia.[30] In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis.[31] With ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme

(xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation. The finding that ischemia results in an increased uric acid levels may account for the increase seen in preeclampsia[32] and congestive heart failure.[33] Other factor, which may also contribute to as why uric acid is associated with hypertension, includes alcohol abuse,[34] lead intoxication,[35] obesity and insulin resistance, and diuretic use.

The observation that an elevated uric acid is associated with subjects at cardiovascular risk may account for hyperuricemia predicting the development of cardiovascular disease in the general population, in subjects with hypertension, and in subjects with preexisting cardiovascular disease. Hyperuricemia also predicts stroke in diabetic and non-diabetic subjects[36,37] and predicts the development of hypertension[38,39,40] and renal disease in the general population.[41] In these studies, uric acid may be simply "marking" subjects at increased cardiovascular and renal risk[42,43] Consistent with this hypothesis, many studies have found that uric acid is not an independent risk factor for cardiovascular disease after controlling these other risk factors. Hyperuricemia is therefore considered benign unless associated with gout or kidney stones.[44] Nevertheless, some studies find uric acid predictive for the development of cardiovascular disease, hypertension, and renal disease despite associated risk factors. This raises the possibility that uric acid may have a pathogenic role in hypertension and cardiovascular disease. Indeed, recently soluble uric acid has been recognized to not be inert but rather to have several biological actions that could either be beneficial or detrimental to humans.

Uric Acid as an Antioxidant: A Protective Factor in Cardiovascular Disease?

An important observation was that uric acid might function as an antioxidant, and possibly one of the most important antioxidants in plasma.[45,46,47] Urate (the soluble form of uric acid in the blood) can scavenge superoxide, hydroxyl radical, and singlet oxygen and can chelate transition metals. Peroxynitrite is a particularly toxic product formed by the reaction of superoxide anion with nitric oxide that can injure cells by nitrosylating the tyrosine residues (nitrotyrosine formation) of proteins. Uric acid can also block this reaction.[48]

Recently, Hink et al[49] reported that uric acid might also prevent the degradation of extracellular superoxide dismutase (SOD3), an enzyme critical in maintaining endothelial and vascular function. SOD3 is an extracellular enzyme that catalyzes the reaction of superoxide anion ($O_2^{-}\cdot$) to hydrogen peroxide (H_2O_2). The removal of $O_2^{-}\cdot$ by SOD3 prevents the reaction and inactivation by $O_2^{-}\cdot$ of the important endothelial vasodilator, nitric oxide (NO). SOD3, by removing $O_2^{-}\cdot$, therefore helps to maintain NO levels and maintain endothelial function. Normally, SOD3 is inactivated in the presence of H_2O_2, suggesting a feedback inactivation of the enzyme. However, uric acid blocks SOD inactivation by H_2O_2 by regenerating SOD3 with the production of a urate radical. This latter radical, although potentially a pro-oxidant, has been found to be markedly less reactive than classic oxidants and can be rapidly regenerated back to urate in the presence of ascorbate.[50]

Ames et al[45] hypothesized that the uricase mutation occurred during early hominoid evolution because the antioxidant action of uric acid may have provided an evolutionary advantage and that this may have accounted for the greater longevity of humans and the great apes compared with most other primates. The increase in serum uric acid in subjects with cardiovascular disease might therefore reflect a compensatory mechanism to counter the oxidative stress that occurs in these conditions.[51] However, this does not readily explain why higher uric acid levels in patients with cardiovascular disease are generally associated with worse outcomes

Is Uric Acid a Mediator of Hypertension and Renal Disease?

Endothelial dysfunction, local oxidant generation, elevated circulating cytokines, and a pro inflammatory state are common in patients with cardiovascular disease.[52] Endothelial dysfunction is often demonstrated by showing an impaired NO release in response to acetylcholine, which results in impaired endothelium-dependent vasodilatation. Oxidants may cause endothelial dysfunction by reacting with and removing the NO. The observation that xanthine oxidase generates oxidants and uric acid in settings of tissue ischemia potentially explains why uric acid is associated with endothelial dysfunction and oxidative stress in conditions such as heart failure and diabetes.[53,54,55] Hyperuricemia is also associated with the activation of circulating platelets, which also may reflect endothelial dysfunction.[56] Allopurinol, which inhibits xanthine oxidase and hence blocks both uric acid and oxidant formation, can reverse the impaired endothelial NO production in

both heart failure and type 2 diabetes.[53,54,55] Allopurinol has also been reported to reduce cardiovascular complications after coronary artery bypass[57,58] and in patients with dilated cardiomyopathy.[59] Although the beneficial effects correlate with the lowering of uric acid in some of these studies, most authorities have hypothesized that the beneficial effect of allopurinol is to reduce oxidative stress.

Uric acid may contribute to endothelial dysfunction. Waring et al [60]have reported that uric acid infusion in healthy humans resulted in impaired acetylcholine-induced vasodilatation in the forearm, thereby documenting impaired endothelial NO release. Serum uric acid and serum nitric oxide levels also vary during the day in a reciprocal pattern, suggesting a pattern of physiological regulation.[61] Recent studies in experimental animal models have also found that mild hyperuricemia inhibits the nitric oxide system in the kidney (see below).

The mechanism by which uric acid impairs endothelial function is not known. However, whereas uric acid is considered an antioxidant, it is also pro-oxidative under certain conditions, especially when other antioxidants are at a low level[62,63]

Uric Acid, Vascular Smooth Muscle Cell Proliferation, and Inflammation

Uric acid also stimulates rat vascular smooth muscle cell proliferation in vitro.[64, 65,66,67,68] Vascular smooth muscle cells do not express a receptor for uric acid but rather have organic anion transporters that allow urate uptake.[68] Once inside the vascular smooth muscle cell, uric acid activates specific

mitogen activated protein kinases (Erk1/2) with the de novo induction of cyclooxygenase-2 (COX-2), local thromboxane formation, and with upregulation of platelet-derived growth factor A (PDGF A) and C-chain and PDGF- receptor mRNA The uric acid induced cell proliferation can be inhibited by blocking any member of this pathway.

Soluble uric acid is proinflammatory. Uric acid stimulates synthesis of monocyte chemo attractant protein-1 (MCP-1) in rat vascular smooth muscle cells by activating p38 MAP kinase and the nuclear transcription factors, NF-B and AP-1.[69] MCP-1 is a chemokine that is important in vascular disease and atherosclerosis.[70] Soluble uric acid also stimulates human mononuclear cells to produce interleukin-1ß, interleukin-6, and tumor necrosis factor (TNF). [71] Infusion of uric acid into mice also leads to a marked increase in circulating TNF- levels.[72]

Experimental Models: Hypertension in Hyperuricemic Rats [75]

Recently, mild hyperuricemia was developed in rats through the use of a uricase inhibitor (oxonic acid). Unlike previous hyperuricemic models, this model was associated with no urate crystal deposition in the kidney and relatively preserved renal function. A remarkable observation, now documented by two different laboratories, was that systemic hypertension developed in hyperuricemic rats after several weeks. The hypertension was associated with increased renin and a decreased neuronal nitric oxide synthase (NOS1) in the juxtaglomerular apparatus. The hypertension was prevented by administration of an ACE inhibitor and to a lesser extent by L-arginine (a substrate for nitric oxide), thereby confirming a key role for renin-

angiotensin and NOS systems in the blood pressure elevation. Hypertension and changes in rennin, NOS1 were prevented by maintaining uric acid levels in the normal range with allopurinol or benziodarone (a uricosuric).

Hyperuricemic rats were also shown to have salt sensitivity (that is, a greater increase in blood pressure for the same sodium load compared with normal rats). An explanation for the mechanism comes from studies in other experimental models that have shown that salt sensitivity may result from preglomerular vascular disease. Experimental models associated with preglomerular vascular disease have renal ischemia, leading to the infiltration of leukocytes into the interstitium that generate local oxidants, altering the balance of local vasoregulatory factors favoring vasoconstriction, and resulting in a reduction in sodium excretion, a shift in pressure natriuresis, and an increase in blood pressure. Elements of this pathway have been demonstrated in a variety of animal models, and the salt sensitivity can be prevented or ameliorated by interrupting this pathway.

Consistent with this pathway of salt sensitivity, chronically hyperuricemic rats have thickening and hypercellularity of the afferent arteriole of the glomerulus, with inward hypertrophic vascular remodeling, leading to an increase in medial thickness and a reduction in lumen diameter. The arteriolopathy occurs independent of blood pressure, although it is dependent on the renin-angiotensin system. In concert with the development of pre-glomerular vascular disease, rats manifest subtle tubulo-interstitial inflammation and fibrosis. Once these renal changes develop, salt sensitivity can be shown. At this point, the kidney is driving salt sensitivity because correction of the elevated uric acid level is no longer protective.

Experimental Hyperuricemia and Renal Injury[75]:

Renal injury also occurred in hyperuricemic rats, consisting of afferent arteriolopathy, mild tubulo-interstitial fibrosis, glomerular hypertrophy, and eventually, glomerulosclerosis and albuminuria. Micropuncture studies documented that this is associated with an increase in glomerular hydrostatic pressure. The renal changes are prevented if serum uric acid is maintained in the normal range with allopurinol.

Experimental hyperuricemia also accelerated injury in established models of renal disease. Hyperuricemia exacerbated cyclosporine nephropathy in rats, resulting in worse tubulo-interstitial injury and arteriolar hyalinosis with increased renin and a greater loss of macula densa NOS1 and renal NOS3 expression. Hyperuricemia also accelerated progression in the remnant kidney model and resulted in higher blood pressure, more proteinuria, worser renal function, and more glomerulosclerosis and tubulo-interstitial fibrosis. These rats also had severe vasculopathy, involving the interlobular artery and afferent arteriole with de novo expression of COX-2 in the blood vessels and increased renal renin expression. The renal changes were significantly improved by reducing uric acid levels with allopurinol.

Do the Experimental Studies Provide New Insights? [75]

The observation that hyperuricemic animals have salt sensitivity and increased blood pressure provided an additional mechanism to explain why the uricase mutation occurred in early hominoid evolution. Thus, the uricase mutation may have provided an evolutionary advantage to early hominoids by maintaining blood pressure under the low sodium dietary conditions of that period.

The observation that experimental hyperuricemia caused hypertension, intrarenal vascular disease, renal disease, and vascular inflammation in rats might also provide the long-sought pathogenic mechanism by which uric acid could cause cardiovascular disease in humans.

Is there evidence that uric acid causes hypertension in humans?

Epidemiological studies showed a continuous relation of serum uric acid with blood pressure that is stronger in younger subjects with some dampening over time, which is consistent with the experimental studies that demonstrated that once sufficient renal injury occurred, animals developed salt-sensitive hypertension regardless of the uric acid levels. Hyperuricemia is also an independent risk factor for predicting the development of hypertension**.** To date, no studies have examined whether lowering uric acid will reduce blood pressure in hypertensive humans, but it should be noted that the above studies suggest that lowering uric acid would be more effective at preventing rather than treating hypertension, for once the intrarenal vascular disease develops, the hypertension would then be expected to be driven by the kidney. Hyperuricemia also correlated with plasma renin activity, and renal renin expression is also increased in hyperuricemic rats.

Does uric acid cause renal disease in humans?

Patients with gout frequently have renal dysfunction (25% to 40% of cases), with histologic injury in the majority. The renal lesion consists of variable degrees of arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis, often

with focal deposition of urate crystals in the outer medulla. Many authorities have ascribed the renal lesion to coexistent hypertension or aging-associated renal disease. However, this type of analysis cannot account for all of the renal injury observed.

Recently, an elevated uric acid predicted the development of renal insufficiency in individuals with normal renal function. Uric acid is an independent predictor for progression in IgA nephropathy. Hyperuricemia also correlates with the development of renal dysfunction in type II diabetes and independently predicts progression in renal transplant patients on cyclosporine. In contrast, it remained unclear if uric acid is a risk factor for progression in subjects with established renal disease. Although experimental studies suggest uric acid may act as a risk factor for progression, in the MDRD study, uric acid was not found to be a risk factor. Furthermore, whereas some studies report an improvement in renal function with the lowering of uric acid in gouty subjects, others have not been able to confirm these findings.

How about the role of uric acid in mediating the systemic inflammatory response and endothelial dysfunction in humans?

As discussed earlier, uric acid infusion into humans causes endothelial dysfunction, and allopurinol improves endothelial dysfunction in subjects with congestive heart failure or diabetes. Uric acid also stimulates the production of cytokines from leukocytes and chemokines from vascular smooth muscle cells. This suggests a potential role for uric acid or for xanthine oxidase in mediating the systemic inflammatory response that is linked to cardiovascular events.

Thus, in experimental and in vitro systems, uric acid appears to have the ability to induce inflammatory and vascular mechanisms that may contribute to rather than protect against the development of cardiovascular disease. The in vivo role of serum uric acid as an independent risk factor for cardiovascular and renal morbidity is controversial. A better understanding of its relationship with pre-clinical organ damage may help clarify the mechanism(s) implicated in the development of early cardiovascular disease. A number of studies have shown that serum uric acid plays a role in the development of cardiovascular morbidity in the general population, as well as in patients with hypertension, type II diabetes, and cardiac or vascular diseases. A meta-analysis of data taken from 8 trials that were performed on hypertensive patients showed that each standard deviation (SD) increment in SUA entails an augmentation of cardiovascular risk that equals what is observed for similar changes in blood pressure or total cholesterol. However, the independent role of SUA as a risk factor has been undergoing debate for years. In fact, mild hyperuricemia is often a concomitant finding of obesity, lipid abnormalities, and insulin resistance, all of which are components of the metabolic syndrome (MS). Accordingly, in some studies on white as well as Asian populations, the direct relationship that is observed between uric acid and cardiovascular mortality weakens or disappears after adjusting for confounding factors. The presence of sub-clinical hypertensive organ damage signals a condition of increased risk for cardiovascular and renal, morbidity and mortality. Thus, the search for left ventricular hypertrophy (LVH), carotid atherosclerosis, and microalbuminuria, which likely reflect both the severity of blood pressure load

and other non-hemodynamic risk factors, is currently recommended as part of global risk assessment. Because the role of SUA in the development of cardiovascular disease is receiving growing attention, a better understanding of its relationship with sub-clinical hypertensive target organ damage (TOD) may help clarify the pathophysiological mechanism(s) underlying this association. The present study was therefore performed to evaluate the association between SUA levels and the presence and degree of pre-clinical organ damage in a group of patients with essential hypertension.

MATERIALS AND METHODS

100 patients with recently diagnosed (within six months) hypertension attending the outpatient clinic of our institution during the study period of January 2004 to December 2005 were included in this study. Diagnosis of essential hypertension was made after complete medical history, physical examination, and routine biochemical analysis of blood and urine. Hypertension was defined according to the JNC VII guidelines.

Exclusion criteria:

1. Patients older than 70 years
2. Hypertension duration > 6 months
3. Diabetes mellitus
4. Cardiac failure
5. Chronic kidney disease
6. Patients on diuretics, ACE inhibitors, Angiotensin receptor blockers
7. Secondary hypertension

Five patients were lost to follow up, 2 patients were excluded as they had dilated cardiomyopathy, and 3 patients were excluded as their creatinine clearance was below 60ml/min.

A written informed consent was obtained from all patients. History regarding the duration of hypertension, the medications being taken, coexisting medical problems, and symptomatology suggestive of ischemic heart disease,

transient ischemic attacks and that of renal involvement were documented. A detailed history of smoking (pack years / smoking index) and alcoholism (number of alcohol units per week was recorded; 1 alcohol unit=300 ml of beer, 100 ml of wine, or 30 ml of liquor) was obtained. A family history of cardiovascular and renal disease was noted. An overall clinical examination was done to exclude major co-morbidities. Examination of the heart and the peripheral pulses including the carotids were made. Abdominal examination was done to look for renal bruit. The blood pressure was measured at the time of enrollment. The average of their BP recorded in the last 6 months, if present was noted. With the patient in a seated position and after a 5-minute rest, BP was measured on the right arm with a mercury sphygmomanometer (cuff size, 12.5x40 cm). The systolic pressure and diastolic pressure were read to the nearest 2 mm Hg. The blood pressure was graded as

- Good control (systolic BP <140 and diastolic BP <90)
- Fair control (systolic BP 140-160 and diastolic BP 90 – 100)
- Poor control (systolic BP >160 and diastolic BP >100).

The presence, type, and extent of hypertensive retinopathy were investigated in a darkened room and under pupil dilatation. Direct ophthalmoscopy was carried out with an ophthalmoscope. The first arteriovenous crossing at least one disc diameter from the disc in each quadrant was selected and assessed for the presence of focal arteriolar narrowing, hemorrhages, exudates, and papilledema. Retinal lesions were classified according to the Keith-Wagner-Barker classification. BMI was calculated with the following formula:

$$\textbf{BMI = weight (kg)/ height}^{\mathbf{2}}\textbf{(m).}$$

Waist and hip measurements were made as per the ATP III guidelines. The Waist: Hip ratio was then calculated. A basic neurological examination was made to exclude focal neurological deficits. The standard laboratory testing for blood glucose, urea, serum creatinine, potassium was done. Creatinine clearance was estimated using the Cockcroft–Gault formula[17] and ideal body weight was used in the formula. Lipid profile was done for all the patients. The LDL cholesterol was calculated using the Friedwald equation. The ratio between total cholesterol and HDL was noted. Urine was examined for protein (using dipstick) and screened under the microscope for deposits. A baseline standard 12 lead ECG was taken. Left ventricular hypertrophy was calculated using the Romhilt -Estes scoring system (RE score) as shown below

Largest R / S wave in limb lead > 20 mm or S wave in V1/V2 or R wave in V5/V6 > 30 mm	3
Strain pattern (without digoxin)	3
Left atrial enlargement	3
Left axis deviation	2
QRS duration > 0.09 sec	1
Intrinsicoid deflection > 0.05 sec	1

A score greater than 5 was taken to indicate left ventricular hypertrophy.

Microalbuminuria:

All patients were subjected to a spot urine microalbumin test using the radio immunoassay kit. An Albumin creatinine ratio was calculated (lab standard Adults < 30mcg/mg creatinine).

Echocardiogram:

Echocardiograms were obtained at rest with patients supine in the left lateral position, using standard parasternal and apical views (Fig.1). LV mass was derived using the formula described by Devereux and associates:

$$\textbf{LV mass (grams)} = 0.80 \times 1.04 [(VSTd + LVIDd + PWTd)^3 - (LVIDd)^3] + 0.6$$

- VSTd is ventricular septal thickness at end diastole
- LVIDd is LV internal dimension at end diastole
- PWTd is LV posterior wall thickness at end diastole

LV mass was corrected for height$^{2.7}$ (LVMI), and expressed in units of grams/meter (g/m$^{2.7}$). The presence of left ventricular hypertrophy was defined for LVMI >51 g/m$^{2.7}$ in either gender[18].

Carotid Ultrasound Scan

The intima-media thickness (IMT) of both carotid arteries was evaluated by US scan as described by Weldelhag[19] The carotid artery was scanned at the bifurcation and at the common carotid artery (CCA). At each longitudinal projection the far-wall IMT was measured at the distal end of the CCA, 10 mm caudally to the point where the near and far walls lose their parallel

configuration. A carotid IMT greater than 10 mm was considered abnormal. Each measurement was calculated by taking the average of three readings**.** As the measurements were done by a single individual inter-observer variations were minimized (Fig.2).

Serum Uric Acid levels (SUA):

Serum uric acid was calculated using the enzymatic calorimetric test with the normal range for adult males being 3.6 – 7 and for adult females being 2.3 – 6.1. Hyperuricemia was defined as SUA > 7 in males and SUA > 6 in females.

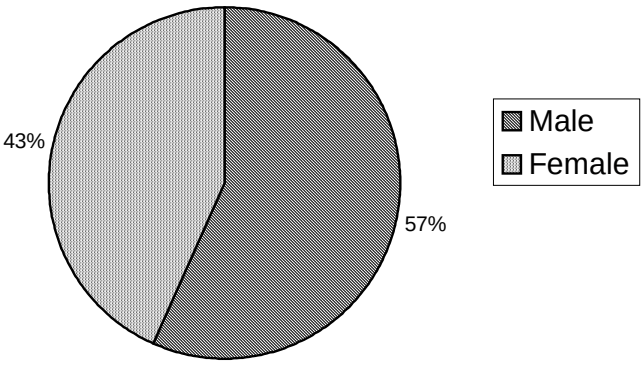
RESULTS OF DESCRIPTIVE STATISTICS

1. Age distribution:

Characteristics	Mean (years)	Distribution (years)
Age	45	30 - 68

2. Sex distribution:

Sex	Numbers (%)
Male	51 (57%)
Female	39 (43%)



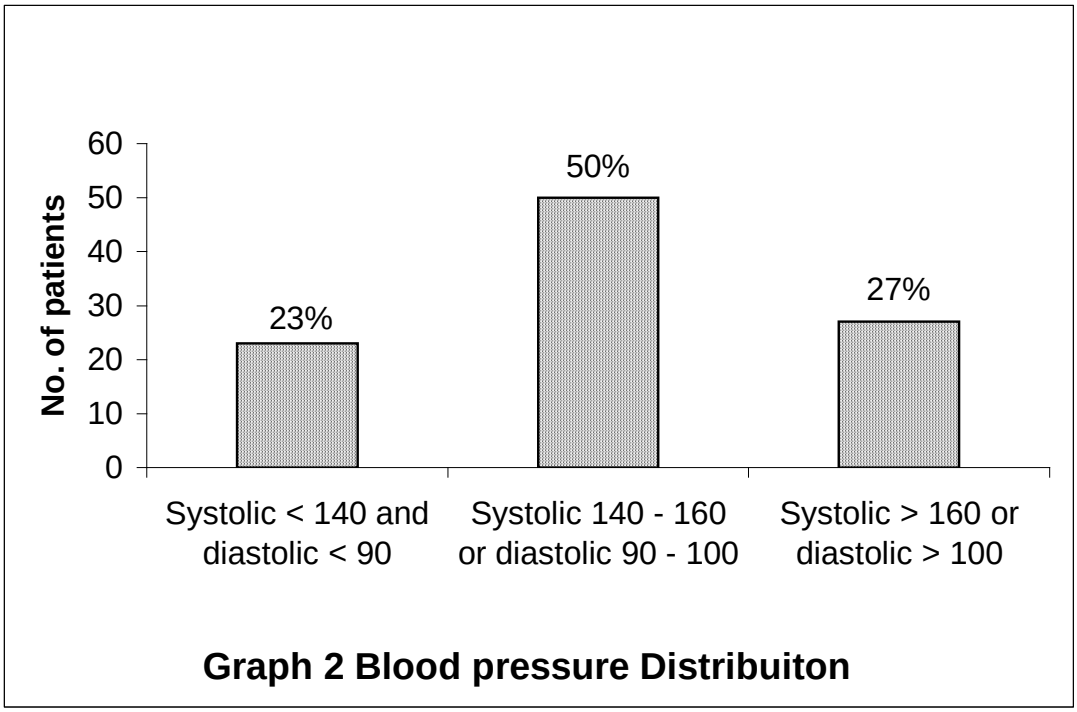
Graph 1 Sex Distribution

3. Menopausal status:

Menopausal state	Numbers (%)
Attained Menopause	12 (30%)
Not attained menopause	27 (70%)

4. Blood pressure distribution:

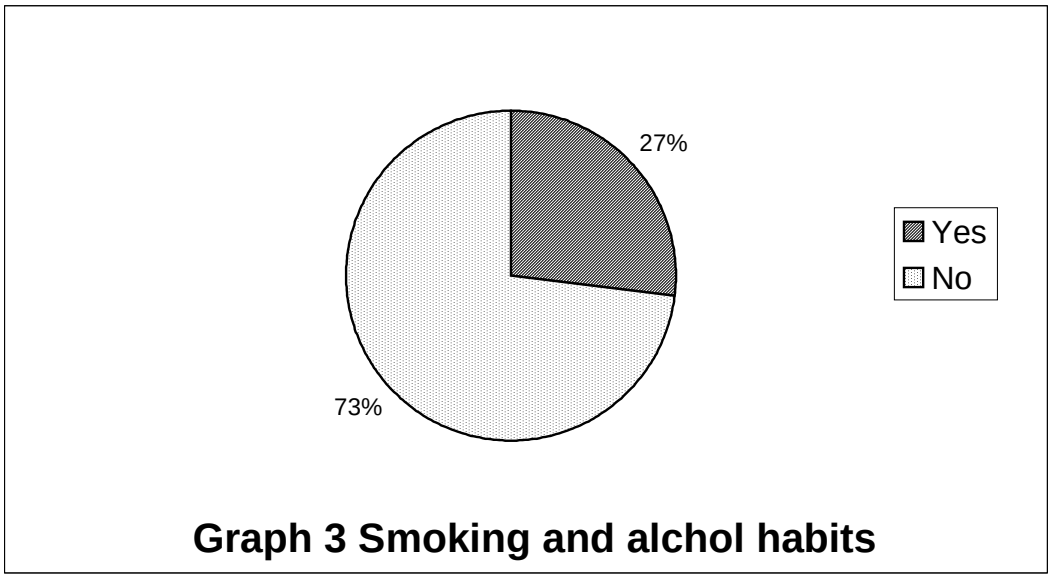
Average Blood pressure	Numbers (%)
Systolic < 140 and diastolic < 90	21 (23%)
Systolic 140 - 160 or diastolic 90 - 100	45 (50%)
Systolic > 160 or diastolic > 100	24 (27%)



Graph 2 Blood pressure Distribuiton

5. Smoking or alcohol habits:

Habits	Numbers (%)
Yes	24 (27%)
No	66 (73%)
Smokers	15 (62%)
Alcoholics	9 (38%)



Graph 3 Smoking and alchol habits

6. Family history of vascular events:

Family history	Numbers (%)
Positive	15(17%)
Negative	75 (83%)

7. Body Mass Index distribution:

Characteristics	Numbers
BMI (mean)	23.42 ± 5.3
BMI (range)	15 - 35
BMI 25 – 30- overweight	9 (10%)
BMI > 30 - obesity	15 (16%)

8. Waist circumference and Waist Hip ratio Distribution:

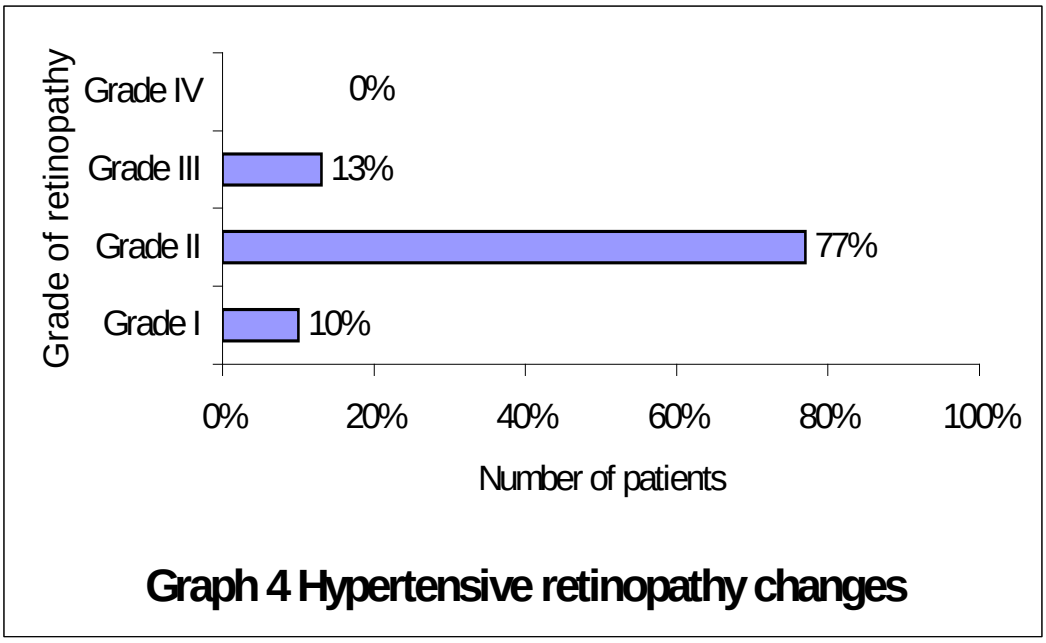
Characteristics	Numbers
Waist circumference (mean)	88 cm ± 11.1
Waist circumference (range)	60 -122 cm
Waist Hip ratio (mean)	0.97 ± 0.1
Waist Hip ratio (range)	0.81 – 1.21
Waist circumference > 90 cm (males)	12 (23% of males)
Waist circumference > 80 cm (females)	27 (69% of females)

9. Lipid distribution:

Characteristics	Numbers
Total cholesterol (mean)	194.8 mg/dl ± 29
Total cholesterol (range)	150 – 272 mg/dl
HDL cholesterol (mean; range)	39.5 mg/dl ± 3.4; 35 – 47 mg/dl
Total cholesterol: HDL ratio (mean; range)	4.97 ± 0.9; 3.3 – 7.16
HDL cholesterol < 40 (males)	24 (47% of males)
HDL cholesterol < 50 (females)	39 (All the females)

10. Hypertensive retinal changes:

Keith Wagner grading	Numbers (%)
Grade I	9(10%)
Grade II	69(77%)
Grade III	12(13%)
Grade IV	0



Graph 4 Hypertensive retinopathy changes

11. ECG evidence of left ventricular hypertrophy:

Romhilt Estes score	Numbers (%)
<= 5	81 (90%)
> 5	9 (10%)

12. Urine Albumin excretion:

Characteristics	Numbers (%)
Urine albumin excretion (mean) (mcg/mg creatinine)	26.8 ± 39
Urine albumin excretion (range) (mcg/mg creatinine)	2.5 – 160
Microalbuminuria present	24 (26%)

13. Left ventricular mass index distribution:

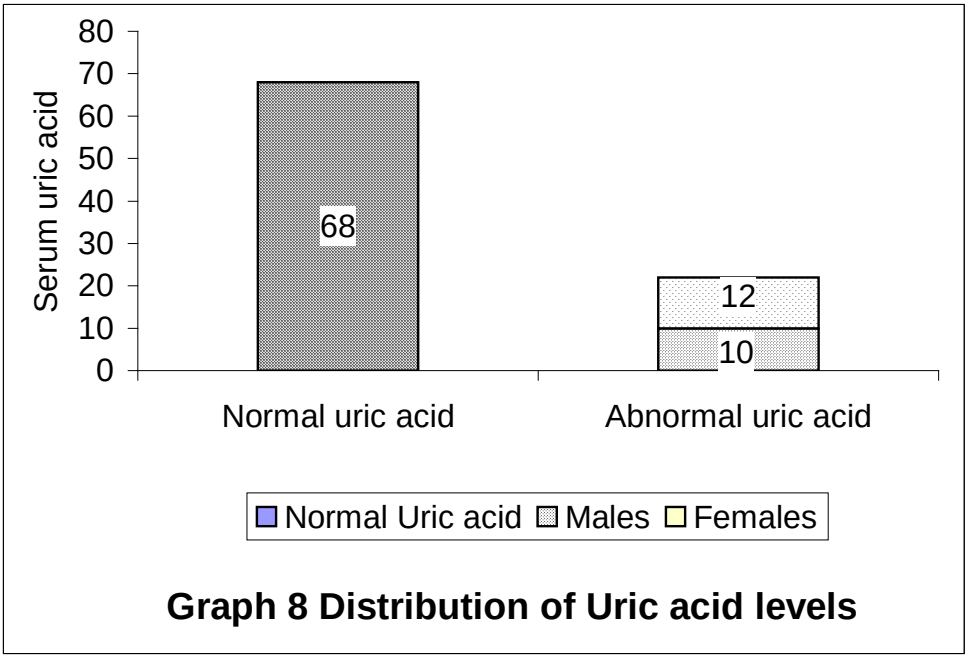
Characteristics	Numbers (%)
LV mass index (mean)	51.8 ± 6.5
LV mass index (range)	44 - 65
LV mass index > 51 (left ventricular hypertrophy)	46 (51%)
LV mass index < 51	44 (49%)

14. Carotid intima media thickness distribution:

Characteristics	Numbers (%)
Carotid IMT > 1 mm (abnormal)	39 (43%)
Carotid IMT < 1 mm	51 (57%)

15. Serum uric acid distribution:

Characteristics	Numbers (%)
Serum uric acid levels (mean)	5.46 ± 1.75
Serum uric acid levels (range)	1.75 – 9.60
Uric acid > 6 (females)	12 (31% of females)
Uric acid > 7 (males)	10 (20% of males)



Graph 8 Distribution of Uric acid levels

CORRELATION OF URIC ACID LEVELS WITH VARIOUS PARAMETERS AND STATISTICAL SIGNIFICANCE

1. Correlation of age with uric acid and indices of target organ damage:

Characteristic	Uric acid	Microalbuminuria	LV mass index	Carotid IMT
Age	- 0.157 (p = 0.139)	-.024 (p = -0.822)	0.147 (p = 0.166)	0.328 (p = 0.002)

Age did not significantly influence the other indices of target organ damage like microalbuminuria, LV mass index. There was a positive correlation between age and the carotid IMT (correlation coefficient 0.328), however age did not significantly influence uric acid levels (cc -0.157).

2. Correlation of sex and uric acid:

Characteristic	Sex	N	Mean uric acid levels	SD	t-test
Uric acid	Male	51	5.7110	1.70863	t=1.6 p=0.11
	Female	39	5.1218	1.76679	

3. Correlation of menopausal state with uric acid:

Characteristic	N	Mean uric acid levels	SD	t- test
Post menopausal	12	5.5787	1.46871	F-1.2 p=0.3
Pre menopausal	27	5.0189	1.86605	

The sex did not statistically influence the levels of uric acid (p = 0.11). Among the female patients there was no significant difference in the uric acid levels between pre-menopausal and post-menopausal groups (p = 0.3)

4. Correlation of family history of vascular events with uric acid levels:

Characteristic	Family history Vascular events	N	Mean uric acid levels	SD	t-test
Uric acid	Yes	6	6.0433	1.68856	T=0.85 p=0.39
	No	84	5.4137	1.75549	

The levels of uric acid was not statistically significant between patients who had a positive family history for vascular events and those who did not (p =0.39).

5. Correlation of habituation to smoking / alcohol to uric acid levels:

Characteristic	Smoker_ alcoholic	N	Mean uric acid levels	SD	F-test
Uric acid	Yes	24	5.9342	1.91753	F-1.6 p=0.11
	No	66	5.2817	1.66502	

The levels of uric acid were not influenced significantly by addiction to alcohol or smoking (p = 0.11)

6. Correlation of average blood pressure with uric acid levels:

Grade of BP control	N	Mean uric acid levels	SD	F-test
1 SBP < 140 and DBP < 90	21	5.1029	1.35	F-1.8 p=0.17
2 SBP 140 – 160 or DBP > 90-100	45	5.3227	1.711	
3 SBP >160 or DBP > 100	24	6.0138	2.04	

7. Correlation of blood pressure control with target organ damage:

Characteristic	Target organ damage	Correlation coefficient (p value)
Average Blood pressure	Microalbuminuria	0.508 (0.0001)
	LV mass index	0.457 (0.0001)
	Carotid IMT	0.359 (0.001)

The average degree of blood pressure control correlated positively with the target organ damage, microalbuminuria (cc 0.508), LV mass index (cc 0.457) and carotid IMT (cc 0.359). There was no statistically significant correlation with uric acid levels (p = 0.17). Interestingly the degree of blood pressure control had a negative correlation with the waist circumference (cc -0.238). The patients with poorer control (systolic > 160 or diastolic > 100) had greater waist circumference.

8a. Correlation of components of metabolic syndrome with uric acid and target organ damage:

Characteristic	Uric Acid (cc / p value)	Microalbuminuria (cc / p value)	LV mass index (cc / p value)	Carotid IMT (cc / p value)
BMI	0.11 (p = 0.303)	0.024 (p = 0.82)	0.003 (p = 0.981)	0.035 (p = 0.743)
Waist circumference	0.068 (p = 0.524)	0.167 (p = 0.115)	0.181 (p = 0.08)	0.155 (p = 0.145)
Total cholesterol	0.115 (p = 0.281)	0.117 (p = 0.274)	0.258 (p = 0.014)	0.223 (p = 0.035)
HDL cholesterol	-0.049 (p = 0.647)	-0.158 (p = 0.137)	-0.145 (p = 0.174)	-0.064 (p = 0.549)

8b. Correlation of Waist circumference with uric acid levels:

Characteristic	Waist circumference	N	Mean uric acid levels	SD	t-test
Uric acid	Abnormal	40	5.6513	1.77706	T=0.75
	Normal	50	5.3578	1.74160	p=0.46

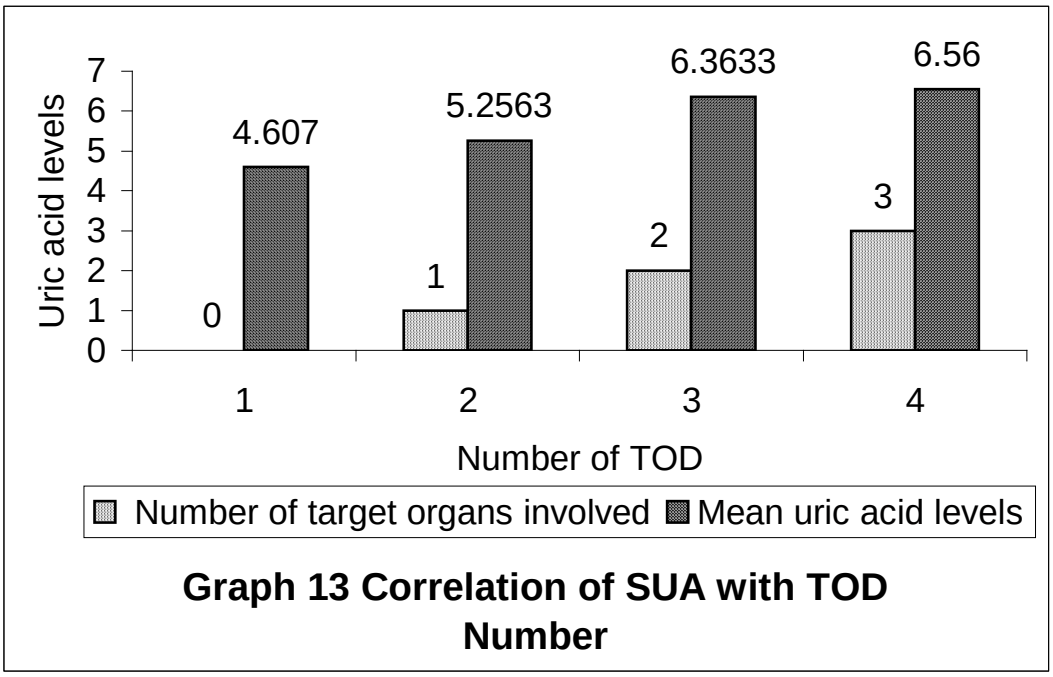
The levels of serum uric acid levels did not correlate with body mass index (p = 0.3), waist circumference (p= 0.52), waist hip ratio (p = 0.7), and the indices of target organ damage also did not statistically correlate with body mass index, waist circumference and waist hip ratio. The total cholesterol levels correlated positively with carotid IMT (cc 0.253) and LV mass index (cc 0.258) but does not correlate with serum uric acid levels (p = 0.28).

9. Correlation of parameters of target organ damage with uric acid levels:

Characteristic	LV mass Index	N	Mean uric acid levels	SD	t-test
Uric acid	Normal	44	4.7264	1.24977	T=4.22
	Abnormal	46	6.1533	1.88155	p=0.001
Characteristic	**Carotid IMT**	**N**	**Mean uric acid levels**	**SD**	**t-test**
Uric acid	Normal	51	4.7582	1.49633	T=4.84
	Abnormal	39	6.3677	1.64688	p=0.001
Characteristic	**Microalbuminuria**	**N**	**Mean uric acid levels**	**SD**	**t-test**
Uric acid	Normal	66	5.1038	1.58699	T=3.34
	Abnormal	24	6.4233	1.84050	p=0.001

10. Correlation of uric acid levels with number of target organs involved:

Number of target organs involved	N	Mean uric acid levels	SD	Std. Error
0	37	4.6070	1.17858	
1	19	5.2563	1.88615	F=8.83
2	12	6.3633	1.64519	p=0.001
3	22	6.5600	1.75021	



Graph 13 Correlation of SUA with TOD Number

Uric acid levels correlated significantly with target organ damage indices (p=0.001). The correlation of uric acid was with LV mass index (cc 0.496) was the strongest when compared with that of microalbuminuria (cc 0.413) and carotid IMT (cc 0.427). Serum uric acid levels positively correlated with number of target organs involved. The greater the number of organs involved the higher the uric acid levels (p= 0.001).

DISCUSSION OF RESULTS

Studies done on the association between serum uric acid levels and the presence and degree of target organ damage are not many. Two studies done in Italy by Francesca Viazzi etal studied the relation of uric acid and target organ damage. The first study investigated the relationship between pulse pressure and sub clinical cardiovascular damage in a cohort of unselected middle-aged patients with untreated primary hypertension (Pulse pressure and sub clinical cardiovascular damage in primary hypertension- Francesca Viazzi etal [73]). The second study aimed to evaluate the association between uric acid levels and the presence and degree of pre clinical organ damage in a group of middle-aged, untreated patients with essential hypertension Serum Uric Acid and Target Organ Damage in Primary Hypertension Francesca Viazzi etal [74]. The results of the present study is compared with the above two studies. Similar studies have not been undertaken in centers in our country.

1a. Comparative Descriptive statistics (Age; Sex)

Parameters	Study on SUA and TOD (n = 425)	Study on SUA and Pulse Pressure (n = 333)	Current study (2006) (n = 90)
Sex(male)	265	204	51
(Female)	160	129	39
Age (yrs)	47±9	47±0.5 (20–66)	45.4 ± 9.49 (30 - 68)
Premenopausal (nos.)	NA	NA	27
Postmenopausal (nos.)	NA	NA	12

1b. Comparative Descriptive statistics (Family history of vascular events; smoking; alcohol; BMI; lipids)

Parameters	Study on SUA and TOD (n = 425)	Study on SUA and PP (n = 333)	Current study (2006) (n = 90)
Family history vascular events (%)	NA	52	16
Smokers (%)	NA	63	62
Alcohol (%)	NA	29	38
BMI kg /m^2	26.4 ± 3.6	17–38 (26 ± 0.2)	15–35 (23 ± 5.3)
Total Cholesterol mg/dl	211.13 ± 1.11	213 ± 2.5	150–272 (194.8 ± 29)
HDL Cholesterol mg/dl	52.97 ± 0.36	52 ± 0.9	35–47 (39.5 ± 3.4)
Prevalence of Metabolic syndrome components (%)	21	NA	NA

The average age of patients in the study was 45.4, which was comparable to the above Italian studies. This study also divided the female population into the pre menopausal and the postmenopausal groups to study if there existed any difference in their cardiovascular and renal target organ damage. However no significant difference was found between the two groups and the mean uric acid levels did not vary (5.01 and 5.17 respectively in premenopausal and postmenopausal) in the two groups. A family history of cardiovascular events was positive in a high number of patients in the study from Italy[1] (52%) when compared to the present study (16%). This could be due to

the lack of awareness and accessibility of pre-symptomatic health screening as well as lack of knowledge regarding the symptomatology of various cardiovascular, cerebrovascular, renal events in our population. The numbers of smokers and alcoholics were comparable. The BMI among the Indian population appear to be lesser than their Italian counterparts. The presence of malnutrition makes BMI a poor marker of health risk in our country. The trend towards using the abdominal circumference as an indicator of vascular risk has been popularized among the Asian population. The mean total cholesterol was higher among the Italian population, however it is to be noted that the HDL cholesterol was at a higher level in these population[1] (52 vs 39). All the women included in the study did not have protective levels of HDL cholesterol (> 50) and hence had one component of metabolic syndrome as per the ATPIII guidelines. However a formal comparison of patients with and without metabolic syndrome was not done in this study. The prevalence of metabolic syndrome in the Italian study was 21%.

1c. Comparative descriptive statistics:

Parameters	Study on SUA and TOD (data on female population)	Study on SUA and PP (n = 333)	Current study (n = 90)
Uric acid (mg/dl)	5.14 ± 0.13	5.1 ± 0.1	5.46 + 1.75
ECG – LVH evidence (%)	13	NA	10
LV mass index	52 ± 2.8	51 ± 0.7	51.81 ± 6.53
LVH – ECHO evidence (%)	43	NA	51
Carotid IMT (mm)	NA	0.68 ± 0.01	1.13
Carotid abnormalities (%)	30	NA	43

The mean uric acid levels were comparable among both the population, 5.1 among the Italians and 5.4 among the Indians. Electrocardiographic evidence for LVH was found in 10 % in the present study, while Echocardiographic evidence was present in 51%. The figures are comparable with the Italian studies. The mean LV mass index was comparable between the two populations. The mean carotid IMT was 1.13 among the study population while it was 0.68 in the Italian group. Carotid abnormalities were seen in 43% of the study population, higher than the Italian studies (30%). This may be due to a higher prevalence of carotid atherosclerosis in Asian population.

2. Correlation of uric acid with target organ damage (Comparative statistics)

Parameters	Study on SUA and TOD (n = 425)	Study on SUA and PP (n = 333)	Current study (n = 90)
Age	Not significant	P < 0.0001	Not significant
Gender	NA	P = 0.04	P = 0.11
HDL cholesterol	P = 0.02	NA	P = 0.647
Microalbuminuria	P = 0.02	P = 0.03	P = 0.001
LV mass index	P = 0.002	P < 0.0001	P = 0.001
Carotid IMT	P = 0.015	P < 0.0001	P = 0.001
Number of target organs involved	P = 0.02	NA	P = 0.001

Serum uric acid levels were correlated with various variables that affected the target organ damage in hypertensive population. Age and sex did not have any significant effect on the uric acid levels, which was also observed in the Italian studies. While HDL cholesterol had a negative correlation with uric acid levels it was not found to be statistically significant. HDL cholesterol correlated with uric acid levels in the Italian studies. In this study serum uric acid correlated significantly with pre clinical target organ dysfunction (i.e.) microalbuminuria, LV mass index and carotid intima media thickness (IMT)**.** These findings were similar to the Italian studies, which had also reported a strong association between uric acid levels and pre clinical organ dysfunction.

Among the target organ dysfunction the strongest correlation was observed between SUA and left ventricular mass index. This confirmed results from previous studies that showed a robust association of uric acid with electrocardiographic abnormalities and coronary atherosclerosis. It is to be noted that confounding factors like age, sex, alcoholism, smoking, BMI, Waist circumference, Waist Hip ratio and dyslipidemia did not correlate with uric acid levels, further suggesting uric acid as an independent marker of cardiovascular and renal abnormalities. Another highlight of the study was the correlation of uric acid levels with the number of target organs involved. This is similar to the report by Francesca Viazzi etal that found a statistically significant relation between the uric acid levels and number of target organs involved. The graphical results were compared (Graphs 13 and 14).

The association between SUA and early hypertensive and atherosclerotic organ damage is intriguing and suggests that mild hyperuricemia might be a marker of incipient cardiovascular involvement. The other aspect brought out by the study was the positive correlation between the average blood pressure control and the influence on the target organ damage. Though it did not correlate with serum uric acid levels, it did emphasize the point that target organ dysfunction primarily depends on adequacy of blood pressure control. This has been emphasized by previous studies by Francesca etal [73,74]. The role of increased pulse pressure in the context of cardiovascular risk assessment and stratification is currently receiving growing attention. Furthermore, elevated pulse pressure values, measured both in the office and by 24-h ambulatory monitoring, have been linked to the

presence of sub clinical cardiovascular damage, i.e. left ventricular hypertrophy, increased carotid wall thickness, and microalbuminuria, as well as to structural changes in the resistance vasculature at the peripheral levels. It has been suggested that high pulse pressure levels reflect the degree of stiffness of the arterial tree, regardless of whether they are caused by increased systolic (SBP) and/or reduced diastolic pressure (DBP). It was interesting to observe that the degree of blood pressure control had a negative correlation with the waist circumference. Insulin resistance could explain this relation and in the context of primary hypertension, mild hyperuricemia is often a feature of insulin resistance and the metabolic syndrome. The current study however did not show any correlation between the metabolic syndrome components (Waist circumference, waist hip ratio, dyslipidemia) and uric acid levels. However a formal comparison was not done between patients who had metabolic syndrome and those who did not. The results suggested that uric acid might be implicated in the early pathogenetic stages of cardiovascular damage. They also provide a pathophysiological rationale to at least partly account for the association of uric acid to cardiovascular events and mortality in hypertensive patients. In fact, sub clinical TOD represents an intermediate step between exposure to risk factors and occurrence of overt cardiovascular disease and has previously been shown to be a strong predictor of major events. Several mechanisms have been proposed to account for the association between SUA and cardiovascular and renal abnormalities, and include: (1) increased uric acid production to counteract oxidative stress and endothelial damage in

the context of the atherosclerotic process (2) the severity of hypertension itself; and (3) a subtle reduction in glomerular filtration rate leading to impaired renal uric acid clearance. The issue of mild hyperuricemia and cardiovascular disease has been getting more and more attention since anti-hypertensive agents were shown to possibly induce subtle but significant changes in uric acid, which could impact on their ability to provide cardiovascular and renal protection. In conclusion the present study showed that increased SUA was a marker of preclinical TOD in a population of patients with primary hypertension.

CONCLUSIONS

- Age, sex, menopausal state did not affect the serum uric acid levels
- The levels of uric acid were not statistically significant between patients who had a positive family history for vascular events and those who did not.
- The levels of uric acid were not influenced significantly by alcohol or smoking
- The average degree of blood pressure control correlated positively with the target organ damage, microalbuminuria, LV mass index and carotid IMT. There was no statistically significant correlation with uric acid levels
- The degree of blood pressure control had a negative correlation with the waist circumference.
- The levels of serum uric acid levels did not correlate with body mass index, waist circumference, waist hip ratio, and the indices of target organ damage also did not statistically correlate with body mass index, waist circumference and waist hip ratio.
- The total cholesterol levels correlated positively with carotid IMT and LV mass index but did not correlate with serum uric acid levels.
- Uric acid levels correlated significantly with target organ damage indices. The correlation of uric acid was with LV mass index was the strongest when compared with that of microalbuminuria and carotid IMT. Serum uric acid levels positively correlated with number of target organs involved. The greater the number of organs involved the higher the uric acid levels.

SUMMARY

The role of serum uric acid as an independent risk factor for cardiovascular and renal morbidity is controversial. A better understanding of its relationship with pre-clinical organ damage may help clarify the mechanism(s) implicated in the development of early cardiovascular disease. The present study aimed to evaluate the correlation between serum uric acid levels and the presence and degree of pre-clinical organ damage in hypertensive population. 100 patients with recently diagnosed hypertension attending the outpatient clinic of our institution were studied. Albuminuria, Left ventricular mass index and carotid intima-media thickness were assessed for all patients. Uric acid levels correlated significantly with target organ damage indices. The correlation of uric acid was with LV mass index was the strongest when compared with that of microalbuminuria and carotid IMT. Serum uric acid levels positively correlated with number of target organs involved. However the direct relationship between uric acid and target organ damage was weakened by factors like dyslipidemia and degree of control of blood pressure, which also determined the target organ dysfunction.

FUTURE DIRECTIONS

Whether SUA is an independent, modifiable marker or a surrogate marker of TOD needs to be studied. Further studies are needed to ascertain whether SUA reduction per se confers cardiovascular protection, and the possible role it may play as a surrogate end point of anti-hypertensive treatment.

ABBREVIATIONS

SUA - Serum uric acid

TOD – Target organ damage

LVH – Left Ventricular hypertrophy

IMT – Intima media thickness

BP – Blood pressure

SBP – Systolic blood pressure

DBP – Diastolic blood pressure

PP – Pulse pressure

SD – Standard Deviation

US – Ultrasound

BMI – Body mass index

WHR – Waist Hip ratio

cc – Correlation co-efficient

CCA – Common carotid artery

PROFORMA

Name

Age

Sex M/F (If Female Menopause attained Y / N)

HTOP No.

DM Y / N

CKD Y/ N

CAD / MI / DCM Y / N

Diuretic use Y / N

Duration of HT

Average BP in past 3 mon.

CVA Y / N

Angina / MI Y / N

Visual disturbance Y / N

Oliguria Y / N

Nocturia Y / N

Pedal edema Y / N

Abdominal pain Y / N

Burning micturition Y / N

Co-morbid conditions:

Smoker type / quantity / duration

Alcohol type / quantity / duration

Family H /o DM / SHT / CAD / CVA / Renal Disease

Examination:

Height Weight Waist Hip

Pulse

Peripheral pulses

Carotids equal / unequal

BP (upper limb)

Fundus

Arteriolar narrowing Y / N

AV changes Y / N

Hemorrhages / cotton wool spots Y / N

Papilledema Y / N

CVS

Per Abdomen:

Bruit: Y / N

Aneurysm: Y / N

Neurological exam (focal neurological deficit) Y / N

Blood Glucose (fasting)

Urea

Serum creatinine

Lipid profile

Urine protein sugar deposits

ECG (RE score) -

Echocardiogram

Carotid intima media thickness:

Albumin creatinine ratio

Serum uric acid

Comments:

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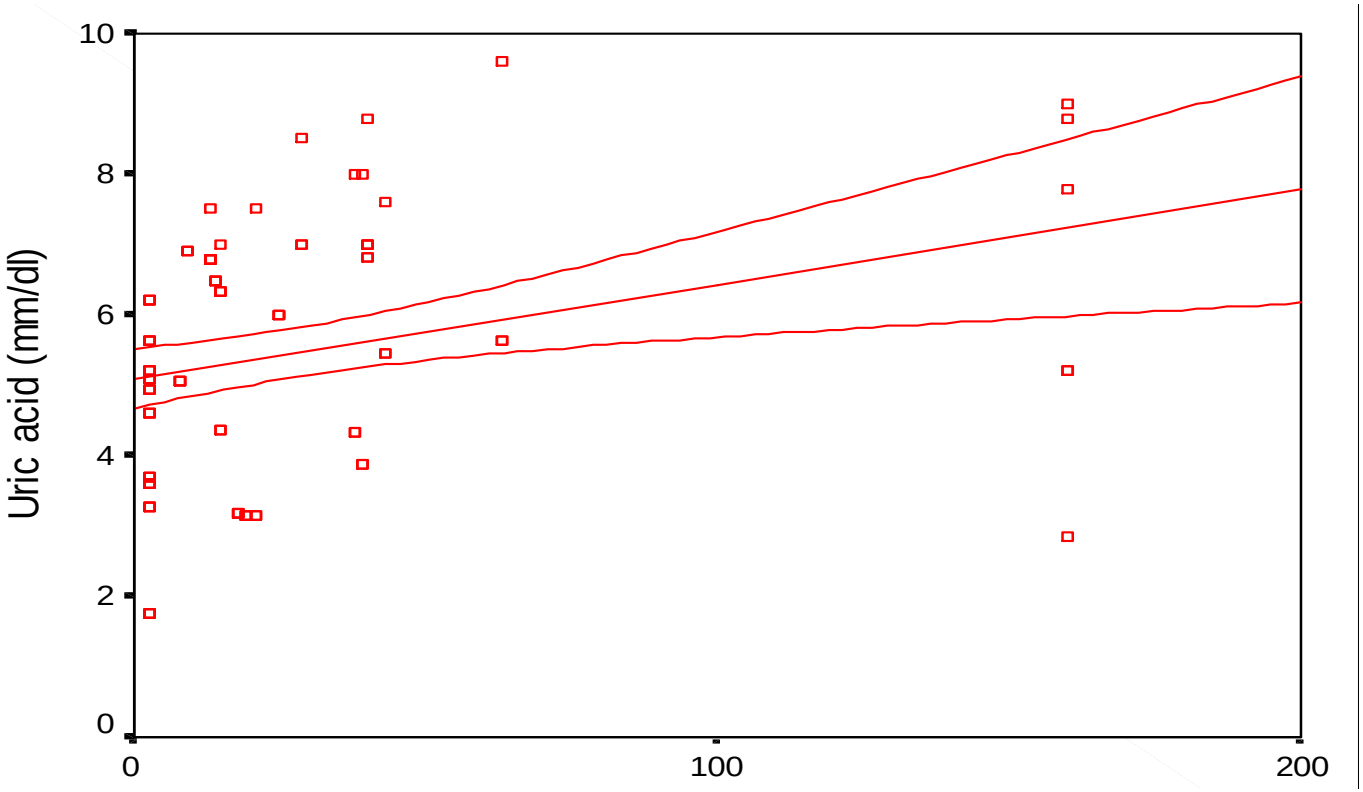
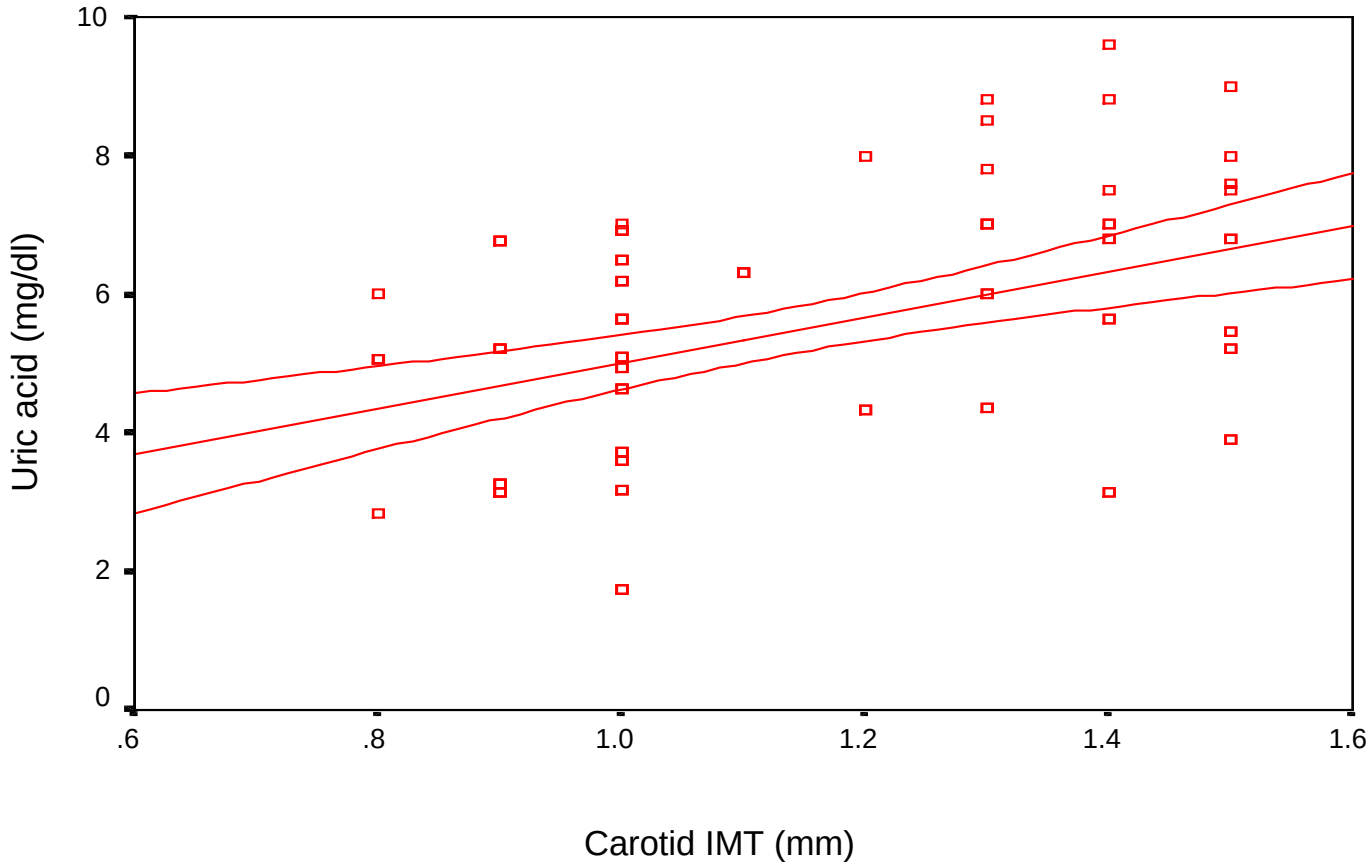
MASTER CHART

S.No.	Name	Age	Sex	Menopausal status	BP – degree of control	Smoker / alcoholic	Family history of vascular events	Ht	Wt	BMI	Waist	Hip	W_H_ ratio	Fundus (KW scoring)	TC	HDL	TC_HDL _ratio	CCr	ECG RE score	ACR	Uric_acid	IMT	LVMI
1	Ambika	38	F	N	2	No	Yes	153	50	21.36	80	66	1.21	2	190	35	5.43	> 90	2	11	5.07	0.8	45
2	Haridas	59	M	NA	2	Yes	Nil	163	58	21.83	92	98	0.94	2	201	45	4.47	> 90	2	28.9	3.14	1.4	58
3	Anandhi	38	F	N	2	No	Yes	153	50	21.36	80	66	1.21	2	190	35	5.43	> 90	2	11	5.07	0.8	45
4	Bakyaraj	39	M	NA	3	Yes	Nil	166.5	66	23.81	76	68	1.12	2	172	38	4.53	> 90	2	57.31	9.6	1.4	65
5	Karna	40	M	NA	2	No	No	160	88	34.38	78	88	0.89	2	150	35	4.29	> 90	4	59	7	1.4	55
6	Balaraman	39	M	NA	3	Yes	Nil	166.5	66	23.81	76	68	1.12	2	172	38	4.53	> 90	2	57.31	5.64	1.4	65
7	Balasubramani	45	M	NA	2	No	No	165	63	23.14	88	94	0.94	2	272	38	7.16	> 90	2	2.76	4.62	1	50
8	Hussain	59	M	NA	2	Yes	Nil	163	58	21.83	92	98	0.94	2	201	45	4.47	> 90	2	28.9	7.5	1.4	58
9	Balu	45	M	NA	2	No	No	165	63	23.14	88	94	0.94	2	272	38	7.16	> 90	2	2.76	4.62	1	50
10	Amaravathy	38	F	N	2	No	Yes	153	50	21.36	80	66	1.21	2	190	35	5.43	> 90	2	11	5.07	0.8	45
11	Gopal	41	M	NA	3	Yes	No	168	58	20.55	88	90	0.98	2	190	40	4.75	> 90	2	37.26	6.79	1.5	59
12	Madasamy	44	M	NA	2	Yes	Nil	165	45	16.53	88	90	0.98	2	220	35	6.29	> 90	3	59.3	6.81	1.4	65
13	Kodhandaraman	42	M	NA	2	Nil	Yes	164	60	22.31	88	91	0.97	2	190	44	4.32	> 90	2	36.34	4.35	1.3	50
14	Ravi	47	M	NA	2	Yes	No	160	56	21.88	85	92	0.92	2	201	39	5.15	> 90	2	<3.48	4.95	1	45
15	Harikrishnan	59	M	NA	2	Yes	Nil	163	58	21.83	92	98	0.94	2	201	45	4.47	> 90	2	28.9	3.14	1.4	58
16	Basha	39	M	NA	3	Yes	Nil	166.5	66	23.81	76	68	1.12	2	172	38	4.53	> 90	2	57.31	5.64	1.4	65
17	Krishna	40	M	NA	2	No	No	160	88	34.38	78	88	0.89	2	150	35	4.29	> 90	4	59	7	1.4	53
18	Karthikeyan	42	M	NA	2	Nil	Yes	164	60	22.31	88	91	0.97	2	190	44	4.32	> 90	2	36.34	7	1.3	50
19	Madhavan	40	M	NA	1	Nil	Nil	157	57	23.12	84	88	0.95	2	214	35	6.11	> 90	2	< 4.59	5.09	1	45
20	Kamarajan	42	M	NA	2	Nil	Yes	164	60	22.31	88	91	0.97	2	190	44	4.32	> 90	2	36.34	4.35	1.3	50
21	Ponnayan	60	M	NA	1	Yes	Nil	165	45	16.53	83	81	1.02	1	188	45	4.18	> 90	1	< 10.67	3.71	1	45
22	Vijaya	45	F	N	1	Nil	No	160	84	32.81	104	119	0.87	1	200	38	5.26	> 90	2	211.53	9	1.5	60
23	Lakshman	54	M	NA	1	No	Nil	159	55	21.76	89	94.5	0.94	2	175	40	4.38	> 90	1	9.18	6.32	1.1	50
24	Michael raj	44	M	NA	2	Yes	Nil	165	45	16.53	88	90	0.98	2	220	35	6.29	> 90	3	59.3	8.8	1.4	65
25	Lawerence	54	M	NA	1	No	Nil	159	55	21.76	89	94.5	0.94	2	175	40	4.38	> 90	1	9.18	6.32	1.1	50
26	Madhesh	40	M	NA	1	Nil	Nil	157	57	23.12	84	88	0.95	2	214	35	6.11	> 90	2	< 4.59	5.09	1	45
27	Ramesh	47	M	NA	2	Yes	No	160	56	21.88	85	92	0.92	2	201	39	5.15	> 90	2	<3.48	4.95	1	45
28	Madivanan	40	M	NA	1	Nil	Nil	157	57	23.12	84	88	0.95	2	214	35	6.11	> 90	2	< 4.59	5.09	1	45
29	Raju	40	M	NA	1	No	No	168	50	17.72	85	86	0.99	2	150	45	3.33	> 90	3	< 6.19	5.22	0.9	45
30	Balakrishnan	45	M	NA	2	No	No	165	63	23.14	88	94	0.94	2	272	38	7.16	> 90	2	2.76	4.62	1	50
31	Syed Khajaji	31	M	N	2	No	Yes	175	73	23.84	91	98	0.93	2	185	42	4.40	> 90	0	9.49	6.48	1	51
32	Lokeshwar Rao	54	M	NA	1	No	Nil	159	55	21.76	89	94.5	0.94	2	175	40	4.38	> 90	1	9.18	6.32	1.1	50
33	Namratha	47	F	Y	2	No	No	145	55	26.16	105	110	0.95	2	170	35	4.86	> 90	2	8.19	3.6	1	50
34	Shaffee	30	M	NA	3	Yes	No	174	67	22.13	96	96	1.00	3	256	38	6.74	> 90	2	56	7	1.3	65
35	Jalaja	56	F	Y	1	No	No	159	59	23.34	94	87	1.08	3	180	40	4.50	> 90	3	<4.06	5.64	1	51
36	Parasuraman	60	M	NA	1	Yes	Nil	165	45	16.53	83	81	1.02	1	188	45	4.18	> 90	1	< 10.67	3.71	1	45
37	Vidya	45	F	N	1	Nil	No	160	84	32.81	104	119	0.87	1	200	38	5.26	> 90	2	211.53	5.22	1.5	60
38	Rajiv	40	M	NA	1	No	No	168	50	17.72	85	86	0.99	2	150	45	3.33	> 90	3	< 6.19	5.22	0.9	45
39	Gokul	41	M	NA	3	Yes	No	168	58	20.55	88	90	0.98	2	190	40	4.75	> 90	2	37.26	6.79	1.5	59
40	Vittal rao	55	M	NA	2	No	No	150	36	16.00	82	79	1.04	2	175	35	5.00	> 90	2	13.11	3.17	1	45
41	Ramar	68	M	NA	3	Yes	Yes	172	80	27.04	103	111	0.93	2	210	40	5.25	> 90	2	58.3	3.89	1.5	58
42	Karuppan	40	M	NA	2	No	No	160	88	34.38	78	88	0.89	2	150	35	4.29	> 90	4	59	7	1	51
43	Ramasamy	40	M	NA	3	No	No	157.5	39	15.72	60	74	0.81	2	164	47	3.49	> 90	6	145	7.8	1.3	55
44	Veera	55	M	NA	2	No	No	150	36	16.00	82	79	1.04	2	175	35	5.00	> 90	2	13.11	3.17	1	45
45	Rakesh	47	M	NA	2	Yes	No	160	56	21.88	85	92	0.92	2	201	39	5.15	> 90	2	<3.48	4.95	1	45
46	Deepa	43	F	N	2	No	No	150	50	22.22	85	94	0.90	2	213	44	4.84	60-90	2	2.4	6.2	1	50

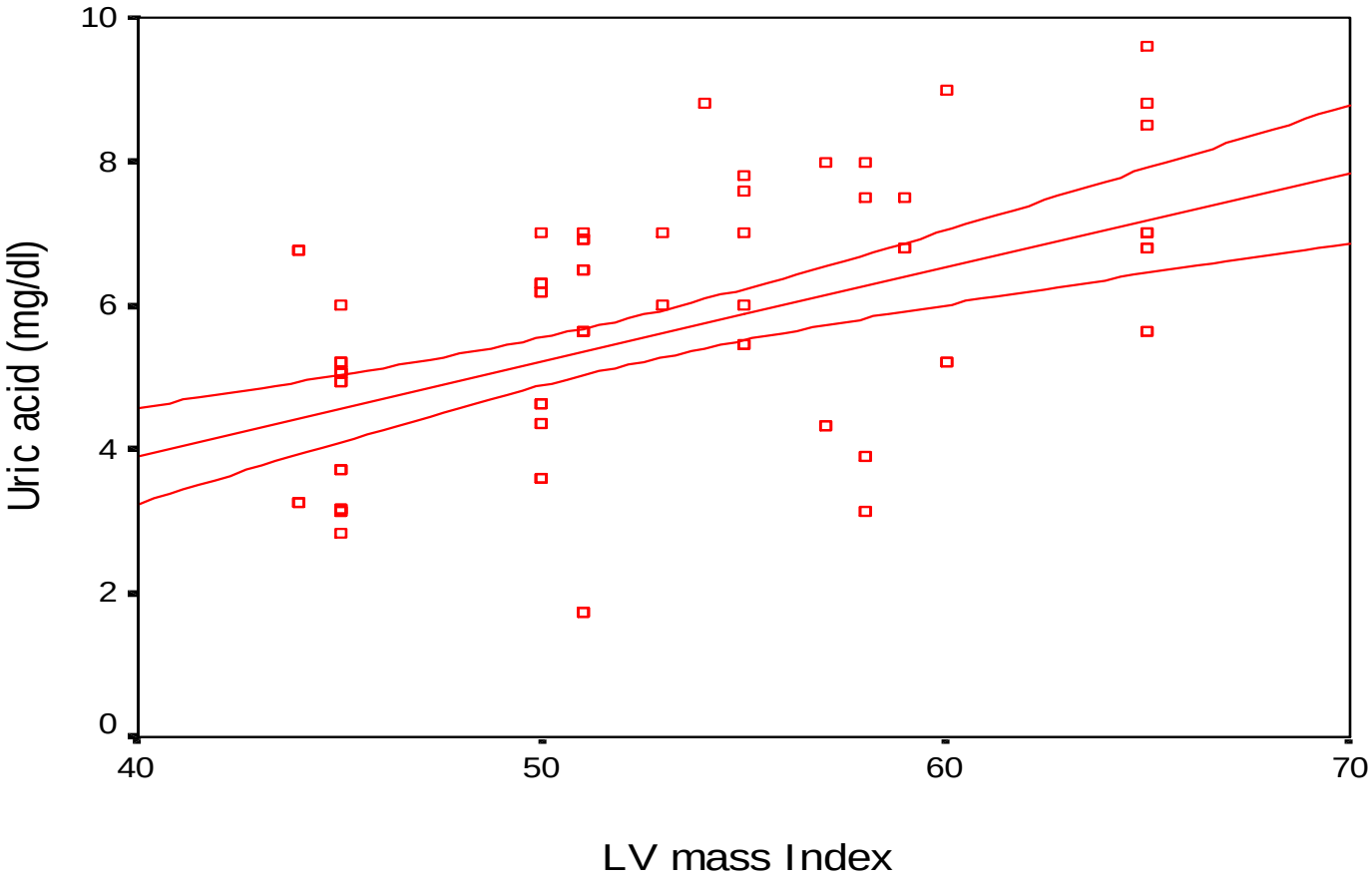
S.No.	Name	Age	Sex	Menopausal status	BP – degree of control	Smoker / alcoholic	Family history of vascular events	Ht	Wt	BMI	Waist	Hip	W_H_ ratio	Fundus (KW scoring)	TC	HDL	TC_HDL _ratio	CCr	ECG RE score	ACR	Uric_acid	IMT	LVMI
47	Lalitha	41	F	N	2	No	Nil	152	52	22.51	89	75	1.19	2	215	40	5.38	> 90	7	2.5	1.75	1	51
48	Saritha	60	F	Y	3	No	Nil	150	35	15.56	80	85	0.94	1	200	35	5.71	> 90	1	60.82	4.34	1.2	57
49	Ragamadulla	68	M	NA	3	Yes	Yes	172	80	27.04	103	111	0.93	2	210	40	5.25	> 90	2	58.3	8	1.5	58
50	Pavithra	35	F	N	2	Nil	Nil	145	65	30.92	75	90	0.83	2	150	40	3.75	> 90	4	45	6	1.3	55
51	Malar	40	F	N	1	Nil	No	168	73	25.86	94	110	0.85	2	170	40	4.25	> 90	2	< 6.19	3.26	0.9	44
52	Saleem	31	M	N	2	No	Yes	175	73	23.84	91	98	0.93	2	185	42	4.40	> 90	0	9.49	6.48	1	51
53	Sarika	60	F	Y	3	No	Nil	150	35	15.56	80	85	0.94	1	200	35	5.71	> 90	1	60.82	4.34	1.2	57
54	Venkatesh	55	M	NA	2	No	No	150	36	16.00	82	79	1.04	2	175	35	5.00	> 90	2	13.11	3.17	1	45
55	Jessica	41	F	N	2	No	Nil	152	52	22.51	89	75	1.19	2	215	40	5.38	> 90	7	2.5	1.75	1	51
56	Krishnaveni	38	F	N	2	Nil	Nil	150	74	32.89	92	112	0.82	2	205	40	5.13	> 90	6	12.87	6.78	0.9	44
57	Lakshmi	47	F	Y	2	No	No	145	55	26.16	105	110	0.95	2	170	35	4.86	> 90	2	8.19	3.6	1	50
58	Gnanambal	43	F	N	2	No	No	150	50	22.22	85	94	0.90	2	213	44	4.84	> 90	2	2.4	6.2	1	50
59	Jyothy	56	F	Y	1	No	No	159	59	23.34	94	87	1.08	3	180	40	4.50	> 90	3	<4.06	5.64	1	51
60	Sumathy	33	F	N	3	No	Yes	152	54	23.37	77	90	0.86	2	179	40	4.48	> 90	2	25	3.15	0.9	45
61	Meenakshi	56	F	Y	2	No	Nil	146	75	35.18	122	102	1.20	3	244	39	6.26	> 90	2	15.03	6.92	1	51
62	Kannamma	35	F	N	2	Nil	Nil	145	65	30.92	75	90	0.83	2	150	40	3.75	> 90	4	45	6	0.8	45
63	Noorinisa	56	F	Y	2	No	Nil	146	75	35.18	122	102	1.20	3	244	39	6.26	> 90	2	15.03	6.92	1	51
64	Sharmila	43	F	N	2	No	No	150	50	22.22	85	94	0.90	2	213	44	4.84	60-90	2	2.4	6.2	1	50
65	Kanmani	38	F	N	2	Nil	Nil	150	74	32.89	92	112	0.82	2	205	40	5.13	> 90	6	12.87	6.78	0.9	44
66	Saranya	33	F	N	3	No	Yes	152	54	23.37	77	90	0.86	2	179	40	4.48	> 90	2	25	3.15	0.9	45
67	Gopi	41	M	NA	3	Yes	No	168	58	20.55	88	90	0.98	2	190	40	4.75	> 90	2	37.26	7.5	1.5	59
68	Mohammed haris	30	M	NA	3	Yes	No	174	67	22.13	96	96	1.00	3	256	38	6.74	> 90	2	56	8.5	1.3	65
69	Latha	41	F	N	2	No	Nil	152	52	22.51	89	75	1.19	2	215	40	5.38	> 90	7	2.5	1.75	1	51
70	Kalyani	35	F	N	2	Nil	Nil	145	65	30.92	75	90	0.83	2	150	40	3.75	> 90	4	45	6	1.3	53
71	Kalaiselvi	47	F	Y	2	No	No	145	55	26.16	105	110	0.95	2	170	35	4.86	> 90	2	8.19	3.6	1	50
72	KhajaVali	31	M	N	2	No	Yes	175	73	23.84	91	98	0.93	2	185	42	4.40	> 90	0	9.49	6.48	1	51
73	Maragatham	40	F	N	1	Nil	No	168	73	25.86	94	110	0.85	2	170	40	4.25	> 90	2	< 6.19	3.26	0.9	44
74	Gnaneshwari	38	F	N	2	Nil	Nil	150	74	32.89	92	112	0.82	2	205	40	5.13	> 90	6	12.87	6.78	0.9	44
75	Bhuaneshwari	40	F	N	1	Nil	No	168	73	25.86	94	110	0.85	2	170	40	4.25	> 90	2	< 6.19	3.26	0.9	44
76	Sangeetha	55	F	Y	3	No	No	150	50	22.22	88	90	0.98	3	215	40	5.38	> 90	2	31.24	5.46	1.5	55
77	Ponny	56	F	Y	1	No	No	159	59	23.34	94	87	1.08	3	180	40	4.50	> 90	3	<4.06	5.64	1	51
78	Ruthina bai	56	F	Y	2	No	Nil	146	75	35.18	122	102	1.20	3	244	39	6.26	> 90	2	15.03	6.92	1	51
79	Parveen	60	M	NA	1	Yes	Nil	165	45	16.53	83	81	1.02	1	188	45	4.18	> 90	1	< 10.67	3.71	1	45
80	Satya	55	F	Y	3	No	No	150	50	22.22	88	90	0.98	3	215	40	5.38	> 90	2	31.24	5.46	1.5	55
81	Rajapriya	60	F	Y	3	No	Nil	150	35	15.56	80	85	0.94	1	200	35	5.71	> 90	1	60.82	8	1.2	57
82	Rajalakshmi	55	F	Y	3	No	No	150	50	22.22	88	90	0.98	3	215	40	5.38	> 90	2	31.24	7.6	1.5	55
83	Sridevi	33	F	N	3	No	Yes	152	54	23.37	77	90	0.86	2	179	40	4.48	> 90	2	25	3.15	0.9	45
84	Magesh kumar	44	M	NA	2	Yes	Nil	165	45	16.53	88	90	0.98	2	220	35	6.29	> 90	3	59.3	6.81	1.4	65
85	Naushad ahamed	30	M	NA	3	Yes	No	174	67	22.13	96	96	1.00	3	256	38	6.74	> 90	2	56	7	1.3	65
86	Vidya	45	F	N	1	Nil	No	160	84	32.81	104	119	0.87	1	200	38	5.26	> 90	2	211.53	5.22	1.5	60
87	Ramasamy	40	M	NA	3	No	No	157.5	39	15.72	60	74	0.81	2	164	47	3.49	> 90	6	145	8.8	1.3	54
88	Ramar	68	M	NA	3	Yes	Yes	172	80	27.04	103	111	0.93	2	210	40	5.25	> 90	2	58.3	3.89	1.5	58
89	Rajiv	40	M	NA	1	No	No	168	50	17.72	85	86	0.99	2	150	45	3.33	> 90	3	< 6.19	5.22	0.9	45
90	Ramasamy	40	M	NA	3	No	No	157.5	39	15.72	60	74	0.81	2	164	47	3.49	> 90	6	145	2.84	0.8	45



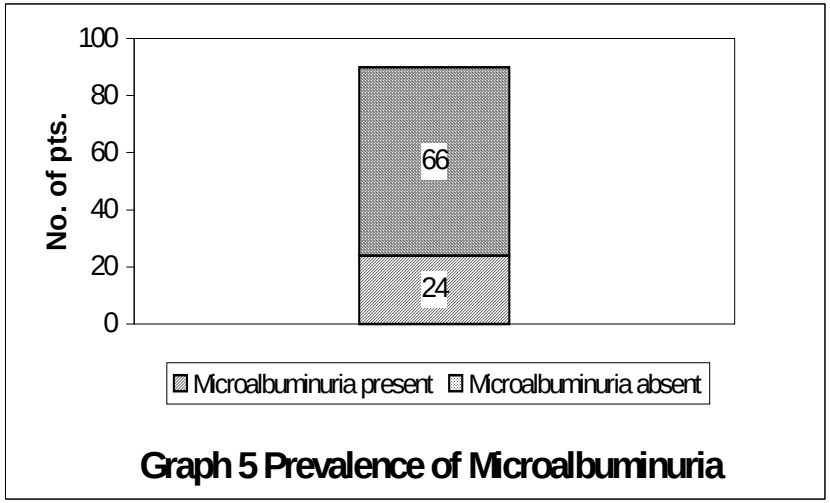
Graph 9 Correlation of Uric acid with Microalbuminuria (mcg/mg)



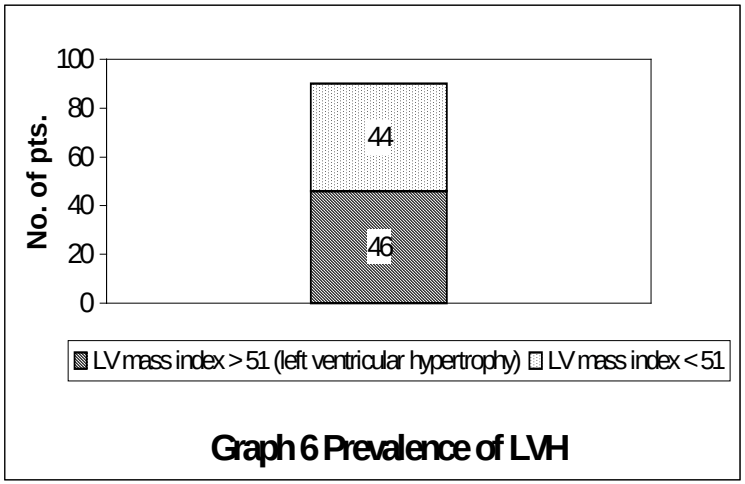
Graph 10 Correlation of Uric acid and Carotid IMT



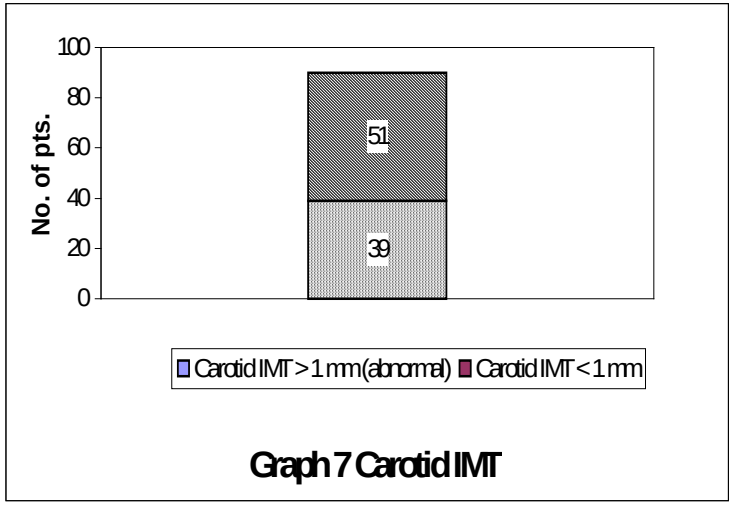
Graph 11 Correlation of Uric acid with LV Mass index



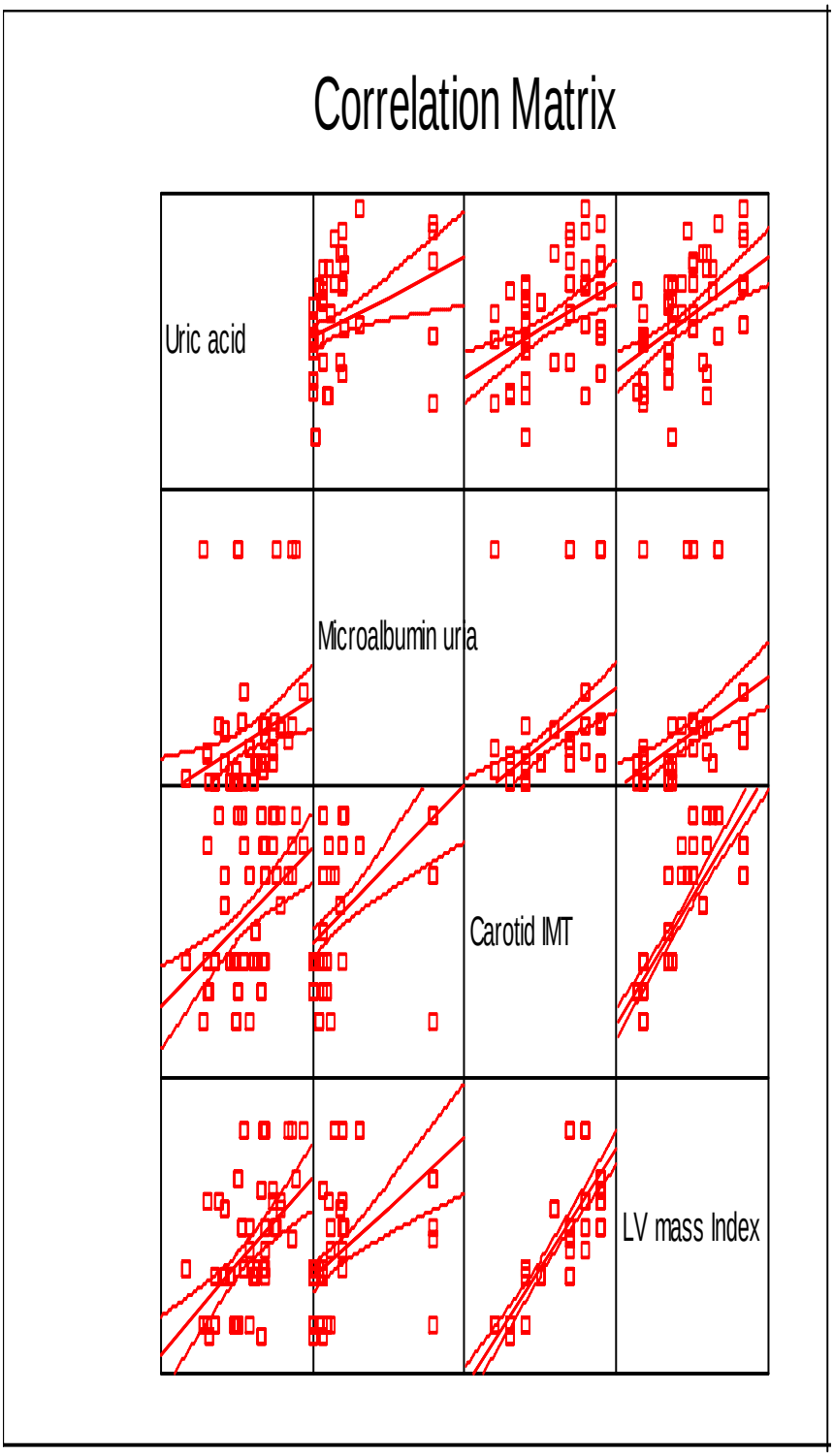
Graph 5 Prevalence of Microalbuminuria



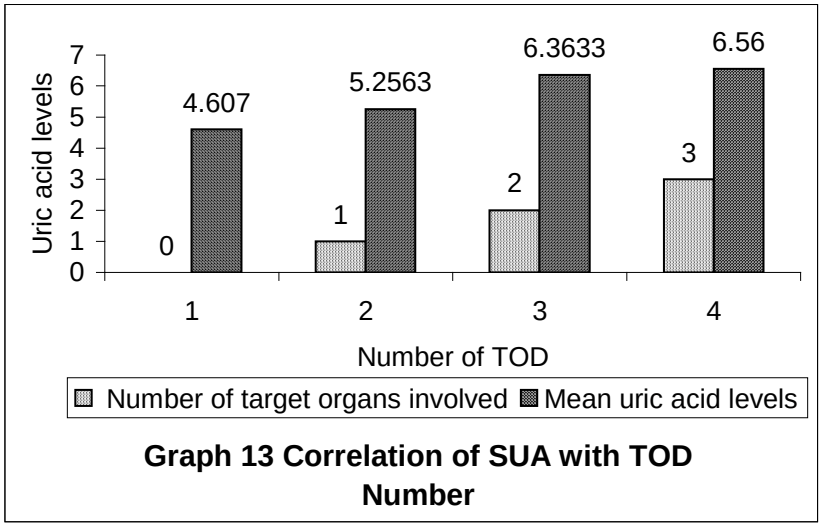
Graph 6 Prevalence of LVH



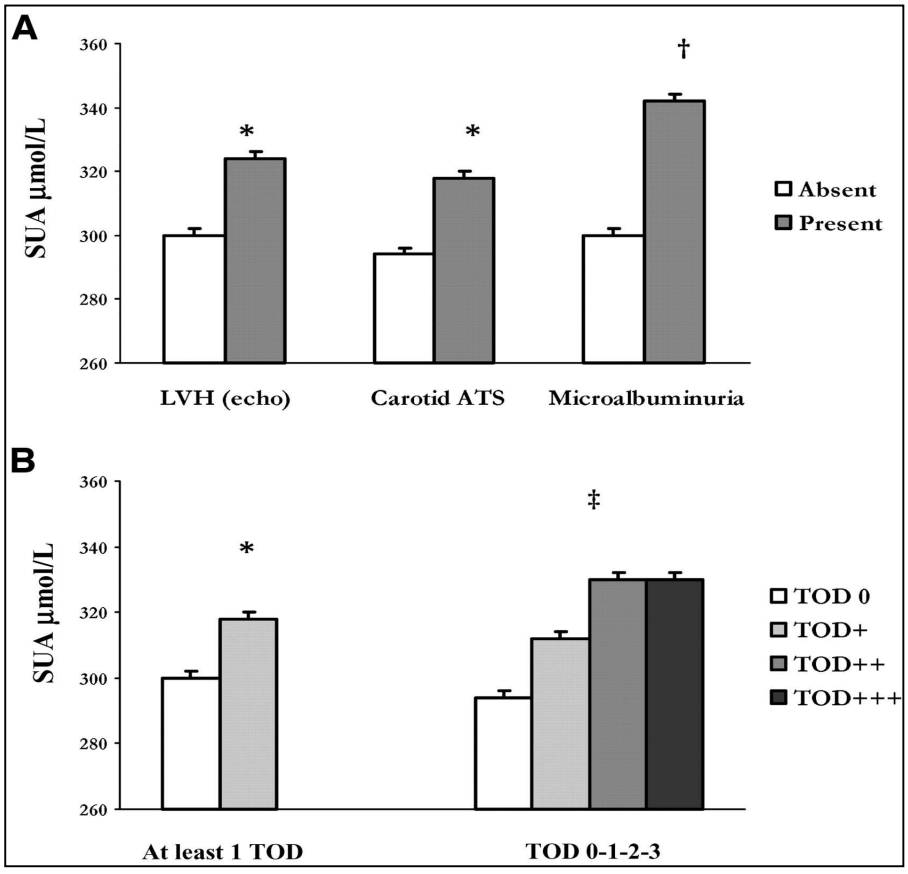
Graph 7 Carotid IMT



Graph 12 Correlation Matrix between Uric acid and TOD



Graph 13 Correlation of SUA with TOD Number



Graph 14 Compared statistics - study by Francesca Viazzi et al

TOD 0, patients without signs of organ damage;
TOD+, subgroup of patients with either LVH or carotid abnormalities or microalbuminuria;
TOD++, patients with a combination of any two signs of TOD;
TOD+++, those with all three signs of the TOD we examined.